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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	27

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/263,689	Ni et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *90-114, 116-121, 124-133, and 136-140* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *90-114, 116-121, 124-133, and 136-140* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Nov 20, 2000* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The request filed on February 11, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/263,689 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 90, 98, 106, 114, 121 and 133 have been amended. Claims 24-27, 68-70 and 77-80 have been canceled. Claims 90-114, 116-121, 124-133 and 136-140 are pending and under consideration.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

4. The rejection of claims 90-114, 116-121, 124-133 and 136-140 under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial asserted utility or a well-established utility is maintained for reasons of record stated in the Office action of Paper No. 14 (mailed February 1, 2001).

Asserted utilities for the SEQ ID NO:4 polypeptide includes the therapy and diagnosis of conditions and diseases characterized by aberrant growth regulatory activity such as autoimmune diseases, cancer, inflammatory disease, wound healing, arteriosclerosis and other heart diseases, microbial infection, asthma and allergic diseases. These asserted utilities of the disclosed SEQ ID NO:4 are based on the observation that SEQ ID NO:4 shares sequence homology with other galectins (figure 5) and in particular, that galectin 1 is known to induce apoptosis of T-cells and T cell leukemias (page 2, lines 22-24 and page 30, lines 8-11), and galectin 3 is known to confer resistance to apoptosis in cultured cells (page 2, lines 27-29). However, there is no evidence in the specification, or any art of record to indicate that SEQ ID NO:4 would be capable of regulating apoptosis in a positive or negative manner, or that the expression of SEQ ID NO:4, or lack thereof, would be diagnostic for any disease state. Clearly the galectins of 1 and 3, although

having the common property of beta-galactoside-binding, exhibit widely differing functions as evidenced by galectin 1 promoting apoptosis and galectin 3 resisting apoptosis. Even if SEQ ID NO:4 or a fragment of SEQ ID NO:4 has the property of binding beta-galactosides, this property does not dictate that SEQ ID NO:4 would function in any apoptotic or stimulatory pathway. The disclosed SEQ ID NO:4 shares sequence homology with other galectins, but also exhibit sequence dissimilarities and the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, Vol. 257, pp.1306-1310, cited in a previous Office action) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (Journal of Cell Biology, 1990, Vol. 11, pp. 2129-2138, cited in a previous Office action) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the growth factor and by Lazar et al (Molecular and Cellular Biology, 1988, Vol. 8, pp.1247-1252, cited in a previous Office action) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply

reduced the biological activity of the altered TGF-alpha. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, the function or tissue distribution of the SEQ ID NO:4 polypeptide could not be predicted, based on sequence similarity with known galectins, nor would it be expected to be the same as that of any of the galectins 1-7. In addition, Bork (Genome Research, 2000, Vol.10, pp.398-400, cited in a previous Office action) teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Given not only the teachings of Bowie et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, the function or tissue distribution of the SEQ ID NO:4 polypeptide could not be anticipated.

The specification discusses the administration of SEQ ID NO:4 for therapy of conditions and diseases characterized by aberrant growth regulatory activity such as autoimmune diseases, cancer, inflammatory disease, wound healing, arteriosclerosis and other heart diseases, microbial

infection, asthma and allergic diseases (page 30, lines 12-18). However, the specification is completely devoid of objective evidence regarding the successful treatment or modulation of any disease in any subject by the administration of the claimed polypeptides. Other asserted utilities for the hypothetical polypeptide of SEQ ID NO:4, such as the production and screening of agonists, antibodies and antagonists apply to many unrelated polypeptide sequences and therefore are not considered "specific" utilities, i.e. they are not specific to SEQ ID NO:4.

The specification suggests on page 49, beginning with line 7, that the polynucleotides encoding the galectins designated as 8, 9, 10 or 10 SV can be used in Northern blot analysis with MTM blots to examine tissue distribution of the disclosed polynucleotides. The specification does not relay any data resulting from the use of the disclosed polynucleotides with actual samples. The linking of the polypeptide of SEQ ID NO:4, with a pathological state is absent from the teachings of the specification.

5. Claims 90-114, 116-121, 124-133 and 136-140 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

6. Applicant has provided the following exhibits and arguments in order to overcome the above rejections.

7. Applicants assert that the polypeptide of SEQ ID NO:4 of the instant invention has utility as it can be used to raise antibodies for the detection of asthma or Hodgkin's disease. Applicants correctly point out that SEQ ID NO:4 is highly homologous to the galectin-9 of Tureci et al (Journal of Biological Chemistry, 1997, Vol. 272, pp. 6416-6422, reference AS of the IDS filed

May 26, 1999) or ecalectin (Matsumoto et al, Journal of Biological Chemistry, 1998, Vol. 273, pp. 16976-16984; Hirashima et al, International Archives of Allergy and Immunology, 2000, Vol. 122 suppl.1, pp. 6-9; Hirashima et al, International Archives of Allergy and Immunology, 1999, Vol. 102 suppl.1, pp. 7-10 and Matsushita et al, Journal of Biological Chemistry, 2000, Vol. 275, pp. 8355-8360). Examination of a protein sequence alignment between the instant SEQ ID NO:4 and Accession Number LEG9_human (Swisprotein Database) indicates that the instant SEQ ID NO:4 is identical to the ecalectin protein sequence (reference 3 of Accession Number LEG9_human, Matsumoto et al, ibid) with the exception of an insertion of 44 amino acids at position 149 of said ecalectin and a serine residue substituted for a glycine residue at amino acid residue position 5 (see documentation for "Conflict" under the Accession Number). The instant SEQ ID NO:4 is also highly homologous to the galectin 9 of Tureci et al with the exception of the same insertion of 44 amino acids at position 149 of said galectin 9, and the further amino acid residue substitutions of lysine for arginine at position 88, serine for phenylalanine at position 135, proline for leucine at position 270 and glutamic acid for glycine at position 313. Matsumoto et al (JBC, 1998) interpreted the small differences in amino acid sequence between ecalectin and galectin-9 as being due to allelic variation of the same human gene (page 16981, column 1, last sentence). Ecalectin has been identified as a T-cell chemo attractant as set forth in the submitted references of Matsumoto et al, 1998,; Hirashima et al, 2000 and 1999 and Matsushita et al 2000. The polynucleotide encoding galectin-9 of Tureci et al was identified from a cDNA library derived from the spleen of a patient suffering from Hodgkin's disease through the SEREX system, wherein said patient had autoantibodies to said galectin-9.

The argument regarding applicants assertion, that the instant SEQ ID NO:4 has utility as it can be used to generate antibodies specifically for the detection of asthma or Hodgkins's disease is not persuasive. Ecalectin/galectin-9 contains an insertion of 44 contiguous amino acids not present in the instant SEQ ID NO:4. Hirashima (1999) discloses that many tissues have been

found to express ecalectin (page 8-9, bridging paragraph) and that this observation is commensurate with tissue eosinophilia. Hirashima further discloses that peripheral blood monocytes taken from patients infected with *Dermatofagoides farinae* produced high levels of ecalectin when stimulated with antigen. Likewise, the peripheral blood monocytes of tuberculin sensitive patients treated with Il-4 also produced high levels of ecalectin (page 9, under the heading "Regulation of Ecalectin Production"). Hirashima (2000) discloses that ecalectin, due to its ability to selectively attract eosinophils, is a target for the treatment of eosinophil-dependent pathological conditions such as allergy, asthma, interstitial pulmonary fibrosis, inflammation in digestive organs, autoimmune disease and malignant neoplasm. Thus, the expression of ecalectin is related to eosinophilia and is not specifically diagnostic for asthma or Hodgkin's disease. Tureci et al disclose that autoantibodies to galectin-9 were detected in 50% of patients having Hodgkin's disease (page 6421, first column, lines 7-12). Thus the detection of an autoantibody to galectin-9 were be diagnostic for Hodgkin's disease in contrast to the detection of the ecalectin/galectin-9 itself, which would not be specifically diagnostic Hodgkin's disease or asthma as the detection of said galectin-9 is indicative of eosinophilia, not specifically Hodgkin's disease or asthma the expression of which would not be confined to asthma of Hodgkin's disease for the reasons set forth above. It is not credible that the instant SEQ ID NO:4, absent 44 contiguous amino acids in comparison with ecalectin/galectin-9, would be used in place of ecalectin or galectin-9 in a process of raising antibodies to ecalectin or galectin-9 as one of skill in the art would raise an antibody which would cross-react with the instant SEQ ID NO:4, and there is no support for the detection of SEQ ID NO:4 and the presence of eosinophilia. It appears from examination of the sequence alignment between the instant SEQ ID NO:4, and the Accession Number LEG9_human, that the instant SEQ ID NO:4 could be a splice variant of ecalectin/galectin-9, but there is no art of record to support the allegation that SEQ ID NO:4 has the same tissue distribution, expression or function as the prior art ecalectin/galectin-9. Hirashima

(2000) discloses that there are multiple isoforms of ecalectin/galectin-9 (page 8, first column second paragraph, lines 10-16), and "it cannot be excluded that each isoform exhibits different biological activity" (page 8, second column, lines 6-7). There are many examples known in the art of differing expression and function between splice variants. For instance, the abstract of Matsushita et al (FEBS Letters, 1999, Vol. 443, pp. 348-352) teaches that latrophilins exhibit alternative splicing resulting in latrophilin-1 which is present in brain and endocrine cells, latrophilin-2 which is ubiquitous, and latrophilin-3 which is brain-specific. The abstract of Singh et al (Glycobiology, 2001, Vol. 11, pp. 587-592) teach that the CD44 splice variant, CD44v, is the major PNA-binding glycoprotein in colon cancer cells in contrast to standard CD44. The abstract of Zwhalen et al (International Journal of Cancer, 2000, vol. 88, pp. 66-70) teaches the expression of p73 splice variants in ovarian adenomas to the exclusion of wild-type p73. These references serve to demonstrate that one of skill in the art cannot anticipate the biological activity or tissue distribution of splice variants based on the biological activity or tissue distribution of the wild-type protein or a single protein isoform. Thus, one of skill in the art would not raise an antibody to SEQ ID NO:4 for the detection of eosinophilia without some teachings supporting the expression of SEQ ID NO:4 in eosinophilic-mediated diseases. Applicants argument regarding the asserted utility of raising an antibody for the detection of Hodgkin's disease is neither specific nor credible as the detection of the ecalectin/galectin protein is not specific to Hodgkin's disease, and the use of SEQ ID NO:4 in place of ecalectin/galectin-9 is not credible given the lack of correlation of SEQ ID NO:4 with eosinophilia.

Applicant argues that ecalectin/galectin-9 are not part of the generalized immune response and said proteins have been used diagnostically for the detection of Hodgkin's disease. The examiner notes that the specification as filed contemplates the detection of SEQ ID NO:4 or the polynucleotides encoding SEQ ID NO:4 for the diagnosis of Hodgkin's disease (page 29, lines 3-24), not the detection of autoantibodies in Hodgkin's patients. It is not a credible assertion that

the instant SEQ ID NO:4, absent 44 contiguous amino acids in comparison with ecalectin/galectin-9, would be used in place of ecalectin or galectin-9 for the detection of Hodgkin's disease. There is no support in the specification or any art of record which would indicate that the serum of Hodgkin's disease patients would bind SEQ ID NO:4 and the serum of normal individuals would not bind SEQ ID NO:4. One cannot exclude the 44 contiguous amino acids present in galectin-9 as comprising the immunogenic epitope(s) responsible for the production of autoantibodies in Hodgkin's patients. If binding to SEQ ID NO:4 is to be used as a surrogate for the detection of Hodgkin's disease, there must be some expression pattern that would allow SEQ ID NO:4 to be used in a diagnostic manner. Therefore, in addition needing to know that SEQ ID NO:4 does bind the autoantibodies found in Hodgkin's disease patients, one need to know that SEQ ID NO:4 will not react with the serum of individuals not affected with Hodgkin's disease. As the expression pattern of SEQ ID NO:4 cannot be inferred from the expression pattern of ecalectin/galectin-9 for the reasons stated above, the asserted utility of being diagnostic for Hodgkin's disease is not credible.

Applicant argues that it is not necessary to provide a molecular mechanism of action regarding the role of SEQ ID NO:4 in asthma or Hodgkin's disease. The examiner agrees that it this is true. However, in the absence of objective evidence regarding the correlation between SEQ ID NO:4 and Hodgkin's disease, a molecular mechanism of action could suffice to overcome the utility rejection. As the instant specification provides neither objective evidence nor molecular mechanism of action, the rejection under 35 U.S.C. 101 is maintained for the reasons set forth in the above.

8. In the event that Applicants might be able to overcome the 35 U.S.C. 101 rejection above, the following rejection would be applied:

102-113, 129, 130.

9. Claims 90, 92, 94-98, 100, 102-114, 116-120, ~~128-131, 133 and 136-140~~ are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to the polypeptides comprising SEQ ID NO:4 and polypeptides consisting of amino acids 62-102, 226-259 and 197-308 of SEQ ID NO:4, does not reasonably provide enablement for polypeptides comprising 30 or 50 contiguous amino acids of SEQ ID NO:4, polypeptides comprising amino acids 62-102, 226-259 and 197-308 of SEQ ID NO:4, proteins comprising amino acid sequences which are at least 95% identical to SEQ ID NO:4 or proteins comprising amino acids which are encoded by polynucleotides that hybridize to SEQ ID NO:3 or the complement thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons of record set forth in the Office action of Paper No. 14 and for the further reasons stated below. 114, 116-120, 131 Ok.

(A)As drawn to proteins comprising amino acid sequences which are at least 95% identical to SEQ ID NO:4

Claims 90, 92, 94-98, 100, 102-105, 128, 129 are drawn to proteins comprising polypeptide variants of SEQ ID NO:4 which bind lactose. Carbohydrate binding domains are recognized in the art (figure 2 of Tureci et al). Although one of skill in the art could generate variants to SEQ ID NO:4 which would not eliminate the lactose binding of the resultant peptide, the effect of alterations of the amino acid sequence in the non-carbohydrate binding portion of SEQ ID NO:4 cannot be anticipated. The relationship between primary amino acid sequence and protein function is probably one of the most unpredictable areas of biotechnology. For example, as disclosed by Burgess et al (ibid), replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while

replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. (Lazar et al, ibid). These references demonstrate that even a single amino acid substitution or what appears to be a small chemical modification will often dramatically affect the biological activity and characteristic of a protein, and the specification gives no guidance on or exemplification of how to make/use the broadly claimed variant polypeptides.

Applicant argues that the amendment of the claims to specify lactose-binding ability renders moot the rejection under 35 U.S.C. 112, first paragraph. Enablement under 112, first paragraph is based on having a specific and substantial use. As all galectins bind lactose, this function is not specific. Hirashima (2000) teaches that recombinant proteins consisting of the N-terminal carbohydrate binding region or the C-terminal carbohydrate binding region of ecalectin exhibited 100-fold less eosinophilic attractant activity in contrast to wild-type ecalectin. Hirashima teaches that a combination of the N-terminal and C-terminal fragments did not reconstitute the eosinophil chemo attractant activity of ecalectin (page 7, second column lines 4-8). Hirashima concludes "From these results, it is suggested that divalent galactoside binding activity is required for eosinophile chemo attraction by ecalectin, and that it is not sufficient to exhibit ECA activity (eosinophil chemo attraction)" (page 7, second column, lines 22-26). Therefore Hirashima teaches that lactose-binding ability is a necessary but not sufficient requirement for eosinophilic chemo attraction. The binding of lactose therefore, cannot be considered a substantial because, as an isolated protein function, it is not key to the eosinophilic chemo attraction activity of ecalectin.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use the variant polypeptides of SEQ ID NO:4 as amendment of the claims to recite lactose binding ability does not narrow the scope of the claims to allow one of skill in the art to practice the claimed invention without undue experimentation.

(B)As drawn to proteins comprising fragments of SEQ ID NO:4

Claims 106-113 and 130 are drawn to isolated proteins comprising amino acid residues 62-102, 226-259, and 197-308 having lactose binding activity. The specification teaches that the fragments of SEQ ID NO:4 consisting of amino acid residues 62-102, 226-259 and 197-308 are antigenic epitopes of SEQ ID NO:4. The specification defines "antigenic epitopes" on page 26, lines 1-2, as "a region of a protein molecule to which an antibody can bind" and differentiates said antigenic epitopes from immunogenic epitopes (page 25, lines 25-30). It is noted that the specification does not teach that these fragments are responsible for lactose-binding activity. The claims, however, are drawn to proteins comprising said epitopes and it cannot be predicted that these sequences, when embedded into a different amino acid context, would still be accessible to reaction with antibodies. Paul (Fundamental Immunology, (text), 1993, pg. 249, column 2, lines 9-17) teaches that accessibility of an antigenic determinant on the surface of the protein is necessary for the antigenic determinant to be bound by the antibody. Paul states that knowledge of the three-dimensional structure is necessary to predict such accessibility. In addition, Paul states that mobility of the putative antigenic determinant within the protein structure is also a determining factor for the binding of the antigenic determinant to an antibody. Given the broadest reasonable interpretation claims 106-113 read on any protein having lactose binding ability comprising the recited amino acid residues. The scope of the claims must be commensurate with the scope of the enablement set forth, and with the exception of the antigenic regions of SEQ ID NO:4 consisting of amino acid residues 62-102, 226-259 and 197-308, the specification gives no guidance on or exemplification of how to use the polynucleotides that encode the broadly claimed polypeptides having lactose binding ability. Given that state of the art with regard to protein chemistry and antigenic determinants as set forth above, and the lack of teachings in the specification, one of skill in the art would be forced into undue experimentation in order to practice the invention as claimed.

Claims 114, 116-120 and 131 are drawn to proteins which comprise 30 and 50 contiguous amino acids of SEQ ID NO:4, said proteins exhibiting a lactose binding property. The specification does not demonstrate that insertion of fragments of the putative SEQ ID NO:4 into a different amino acid context would result in a polypeptide having the asserted utility of being diagnostic for Hodgkin' disease or asthma. Even if SEQ ID NO:4 was specifically correlated to Hodgkin's disease or asthma, it cannot be anticipated that peptides comprising fragments of SEQ ID NO:4 would have the same use or expression as SEQ ID NO:4. The art teaches that proteins are folded 3-dimensional structures, the function and stability of which are directly related to a specific conformation (Mathews and Van Holde, Biochemistry, 1996, pp. 165-171). In any given protein, amino acids distant from one another in the primary sequence may be closely located in the folded, 3-dimensional structure (Mathews and Van Holde, Biochemistry, 1996, pp. 166, figure 6.1,). The specific conformation of a protein results from non-covalent interactions between amino acids, beyond what is dictated by the primary amino acid sequence. A different amino acid sequence surrounding a fragment of the SEQ ID NO:4 polypeptide can potentially profoundly alter the three dimensional structural environment in which the given fragment is located (Matthews, B. "Genetic and Structural Analysis of the Protein Stability Problem", page 6, second column, first paragraph, In:Perspectives in Biochemistry, Vol. 1, pp. 6-9,). Thus, the consequences of the altered sequence environment on the fragment cannot be predicted. Additionally, it is recognized in the art that protein function is context dependent, and cellular aspects, such as membrane anchorage, protein activation and sub-cellular location must be considered with respect to protein function in addition to molecular aspects (Bork, p. 398, col 2). Given the state of the art regarding the relationship between primary amino acid sequence, structure and function of proteins, and the lack of teachings in the specification, one of skill in the art would be subject to undue experimentation in order to make and use the broadly claimed proteins.

w/d

(C)As drawn to proteins encoded by polynucleotides which hybridize to the protein coding region of SEQ ID NO:3 or the complement thereof.

Claims 133-140 encompass proteins having lactose binding ability, said proteins comprising amino acid sequences encoded by polynucleotides comprising non-disclosed nucleic acid sequences attached to polynucleotides that encode SEQ ID NO:4, that is polynucleotides that hybridize to SEQ ID NO:3 and the complement thereof, under specific hybridization conditions. . Listing the hybridization conditions is not limiting. When given the broadest reasonable interpretation, the claims are clearly intended to encompass a variety of polypeptide variants and it would be expected that a substantial number of the hybridizing or complementary polynucleotides encompassed by the claims would not encode protein which would share either the asserted functional property of being diagnostic for Hodgkin's disease or asthma as attributed to SEQ ID NO:4. In addition, amendment of the claims to specify a protein having lactose binding ability As stated in section (A) above, recitation of the non-specific function of binding lactose does not provide a specific and substantial enablement for the variants polypeptides claimed.. Enablement under 112, first paragraph is based on having a specific and substantial use. As all galectins bind lactose, this function is not specific. Further, Hirashima (2000) teaches that lactose-binding ability is necessary but insufficient for eosinophilic chemo attraction, for the reasons set forth above.. The binding of lactose therefore, cannot be considered a substantial because, as an isolated protein function, it is not key to the eosinophilic chemo attraction activity of ecalectin. Therefore given the broadest reasonable interpretation the claims read on any protein encoded by a polynucleotide which hybridizes to the complement of SEQ ID NO:3, wherein said protein has lactose binding ability. The recombinant proteins consisting of the N-terminal or C-terminal regions of ecalectin (as taught by Hirashima (2000)), would hybridize to the complement of the polynucleotide encoding ecalectin. However, said recombinant proteins have 100-fold less eosinophile chemo attractant ability when compared to wild-type ecalectin (page 7, lines 4-6).

The specification fails to provide an enabling disclosure for how one would use proteins encoded by nucleic acids which hybridize to SEQ ID NO:3 as their is no correlation between the hybridization, the lactose binding ability and the asserted activity of being diagnostic for Hodgkin's disease or asthma. The specification provides insufficient guidance with regard to these issues and provides no working examples which would give guidance to one skilled in the art on how to use the broadly claimed species. For the above reasons, undue experimentation would be required to practice the broadly claimed invention.

New Grounds of Rejection

10. Claims 121, 124, 125 and 132 are rejected under 35 U.S.C. 102(b) as being anticipated by Oda et al (Journal of Biological Chemistry, 1993, Vol. 268, pp. 5929-5939, reference AS on page 5 of the IDS filed May 26, 1999) as evidenced by Accession Number A46631. Claim 121 is drawn to an isolated protein comprising a fragment of SEQ ID NO:4, wherein said protein has lactose binding activity. Claim 124 embodies the protein of claim 121 produced by a host cells. Claim 125 is drawn to a method for producing the protein of claim 121 comprising culturing a host cell under conditions suitable to produce the protein and recovering said protein from the cell culture. Claim 132 is drawn to an isolated protein produced by a method comprising expressing the protein of claim 121 in a cell and recovering the protein.

Oda et al disclose a recombinant protein comprising a fragment of SEQ ID NO:4, as evidenced by the alignment with Accession Number A46631. Oda et al disclose a method for producing a proteins comprising a fragment of SEQ ID NO:4 from amino acid residue 57 to 66,, wherein said protein has lactose binding ability. Oda et al disclose the expression of domain I of L-36 in E coli, said domain corresponding to amino acids 1-150 of L-36 having lactose binding ability (page 5934, column 2, under the heading "Expression of Domain I in E coli"). Oda et al further disclose that the expressed protein was isolated and recovered by gel filtration and further

isolated by isoelectric focusing. The domain I of Oda et al consisting of amino acids 1-150 of L-36 is a protein comprising the fragment of amino acids 57-66 of the instant SEQ ID NO:4.

11. Claims 121, 124-126 and 132 are rejected under 35 U.S.C. 102(b) as being anticipated by Mehul et al (Journal of Biological Chemistry, 1994, Vol. 269, pp. 18250-18258) as evidenced by Accession Number A54909. The embodiments of claims 121, 124, 125 and 132 are set forth above. Claim 126 specifically embodies the protein of claim 121 which comprises a heterologous polypeptide. Mehul et al disclose a method for producing a protein comprising a fragment of SEQ ID NO:4 from amino acid residue 55 to 66, wherein said protein has lactose binding ability. Mehul et al disclose the expression of recombinant CBP30 in E coli. Mehul et al disclose the cloning of the cDNA encoding CBP30 into the PTM-N vector, the expression of said cDNA from said vector resulting in a fusion protein comprising a hydrophobic signal sequence for the exportation of the expressed protein into the periplasmic space of the transformed bacteria (page 18251, column 1, last full paragraph). Mehul et al disclose that the recombinant CBP30 protein was readily recovered from periplasmic contents by affinity chromatography on asialofetuin-Sepharose and eluted from the column by lactose (page 18253, second column lines 20-23. Thus Mehul et al teach that the recombinant fusion protein bound lactose as lactose was able to disrupt the interaction between the recombinant CBP30 protein and the affinity column. Accession number A54909 provides evidence that the CBP30 protein comprises amino acids 55 through 66 of SEQ ID NO:4.

12. Claims 121, 127 and 132 are rejected under 35 U.S.C. 102(b) as being anticipated by Foddy et al (Journal of Cell Science, 1990, Vol. 97, pp. 139-148) as evidenced by Mehul et al (Journal of Biological Chemistry, 1994, Vol. 269, pp. 18250-18258) and Accession Number A54909). Claim 121 is drawn to an isolated protein comprising a fragment of SEQ ID NO:4,

wherein said protein has lactose binding activity. Claim 132 is drawn to an isolated protein produced by a method comprising expressing the protein of claim 121 in a cell and recovering the protein. Claim 127 is drawn to a composition comprising the protein of claim 121 and a pharmaceutically acceptable carrier. The specification defines "pharmaceutically acceptable carrier" to include "formulation auxiliary of any type" (page 32, lines 7-9). Foddy et al disclose a pharmaceutical composition comprising the carbohydrate binding protein of BHK21 cells and Freund's adjuvant for injection into rabbits (page 140, second column, under the heading, "Antibodies"). Foddy et al do not disclose that the carbohydrate binding protein of BHK21 cells is a protein comprising a fragment of SEQ ID NO:4. Mehul et al disclose that intact CPB30 was isolated from BHK cells and cites Foddy et al as the reference (page 18255, first column, lines 2-3 and reference 1). As Freund's adjuvant is pharmaceutically acceptable and also falls within the definition of carrier set forth in the specification ("formulation auxiliary of any type"), Foddy et al disclose the limitations of claims 121 and 127. Claim 132 is drawn to the protein of claim 121 produced by a recombinant expression system. It appears that the claimed protein produced recombinantly is identical to the protein that is expressed in the native BHK cell. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the intact CBP30 protein of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art . See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

13. All other rejections and objections as stated in Paper No. 17 are withdrawn.

14. All claims are rejected.

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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